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DERIVATIVES OF 2-ARYLCYCLOPROPYLAMINE: SYNTHESIS AND INTERACTIONS WITH 5-HT$_{1A}$ RECEPTORS.

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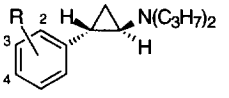
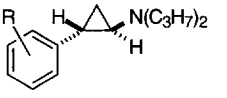
Abstract: A series of *cis*- and *trans*-derivatives of 2-aryl-*N*,*N*-dipropylcyclopropylamines and 1-(2-arylcyclopropyl)-*N*,*N*-dipropylmethylamines were synthesized and evaluated for affinity at the 5-HT$_{1A}$ receptor. The key step in the syntheses was a cyclopropanation of *cis*- and *trans*-3-arylpropenoic esters with diazomethane which proceeds with retention of the stereochemistry. *cis*-1-[2-(3-Methoxyphenyl)cyclopropyl]-*N*,*N*-dipropylmethylamine (**32**) had the highest 5-HT$_{1A}$-receptor affinity (K_i= 58 nM) of the novel derivatives.

The *trans*-2-arylcyclopropyl derivatives **1** - **4** have been characterized as potent 5-HT$_{1A}$ receptor agonists on the basis of *ex vivo* biochemical and behavioural studies in rats.[1] In contrast, the 4-hydroxy (**5**) or 3,4-dihydroxy (**6**) substituted derivatives appeared to be unable to stimulate the 5-HT$_{1A}$ receptors. The activity of **1** and **2** resides predominantly in the 1*R*,2*S* enantiomers.[1,2]



(1*R*,2*S*)-**1**: R = 2-OH
(1*R*,2*S*)-**2**: R = 3-OH
(1*R*,2*S*)-**3**: R = 2-OCH_3
(1*R*,2*S*)-**4**: R = 3-OCH_3

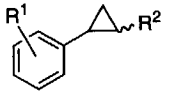


(±)-**5**: 4-OH
(±)-**6**: 3,4-$(OH)_2$

In order to further explore the structure-activity relationships in the arylcyclopropylamine series, we have now synthesized the *cis*- and *trans*-isomers of a series of homologues having the cyclopropane ring and the nitrogen separated by one methylene group (Table 1).[3] In addition, we have synthesized compounds **27** and **28** (Table 1), the *cis*-diastereoisomers of **3** and **4**. The compounds were evaluated for their ability to compete for [^{3}H]-8-OH-DPAT labelled 5-HT$_{1A}$ receptors in rat brain hippocampal membranes (Table 3).

The *trans* derivatives **9** - **11** were prepared from the previously reported[1] carboxylic acids **7** and **8** (Scheme 1); the corresponding acid chlorides were treated with diethylamine or dipropylamine and the resulting amides were reduced with $LiAlH_4$ (Method A). Demethylation of **9** - **11** with BBr_3 (Method B) provided phenols **12** - **14**.

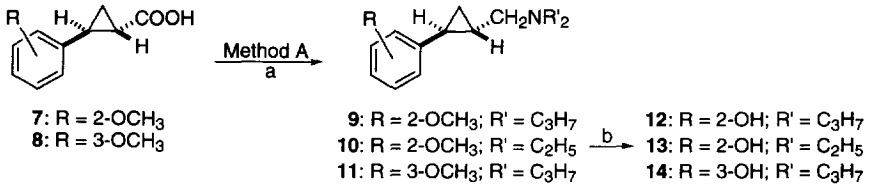
Table 1. Physical data of some racemic arylcyclopropane derivatives.



Compd	Relative stereochem	R^1	R^2	Prepn method	Yield %	Recrystn[a] solvent	Mp °C	Formula[b]
9	trans	2-MeO	CH_2NPr_2	A	61	1	96.5-98	$C_{17}H_{27}NO{\cdot}HCl$
10	trans	2-MeO	CH_2NEt_2	A	84	2	118-120	$C_{15}H_{23}NO{\cdot}HCl$
11	trans	3-MeO	CH_2NPr_2	A	76	2	92-93	$C_{17}H_{27}NO{\cdot}HCl$
12	trans	2-OH	CH_2NPr_2	B	73		oil	$C_{16}H_{25}NO{\cdot}C_2H_2O_4$
13	trans	2-OH	CH_2NEt_2	B	81		oil	$C_{14}H_{21}NO{\cdot}C_2H_2O_4{\cdot}1/4\ H_2O$
14	trans	3-OH	CH_2NPr_2	B	84	2	119.5-120.5	$C_{16}H_{25}NO{\cdot}C_2H_2O_4$
21	cis	2-MeO	COOH	C	46	3	144-145	$C_{11}H_{12}O_3$
22	cis	3-MeO	COOH	C	53	c	92-93[d]	$C_{11}H_{12}O_3$
23	cis	2-MeO	NH_2	D	63	2	178-180	$C_{10}H_{13}NO{\cdot}HCl$
24	cis	3-MeO	NH_2	D	71	2	118-121.5	$C_{10}H_{13}NO{\cdot}C_2H_2O_4$
27	cis	2-MeO	NPr_2	E	62	c	135-138	$C_{16}H_{25}NO{\cdot}HCl$
28	cis	3-MeO	NPr_2	E	46	c	90-93.5	$C_{16}H_{25}NO{\cdot}HCl$
29	cis	2-MeO	CH_2NPr_2	A	50	2	115.5-117.5	$C_{16}H_{25}NO{\cdot}C_2H_2O_4$
30	cis	3-MeO	CH_2NPr_2	A	37	4	78-80.5	$C_{17}H_{27}NO{\cdot}C_2H_2O_4$
31	cis	2-OH	CH_2NPr_2	B	94		oil	$C_{16}H_{25}NO{\cdot}C_2H_2O_4{\cdot}1/2\ H_2O$
32	cis	3-OH	CH_2NPr_2	B	49	5	159-161	$C_{16}H_{25}NO{\cdot}C_2H_2O_4$

[a]1= MeCN/ether, 2= MeOH/ether, 3= acetone, 4= MeOH/*t*-butylmethylether, 5= MeOH. [b]The elemental analyses (C, H and N) for all new compounds were within 0.4 % of the theoretical values. [c]Not recrystallized. [d]Literature mp 101-103 °C, ref 4.

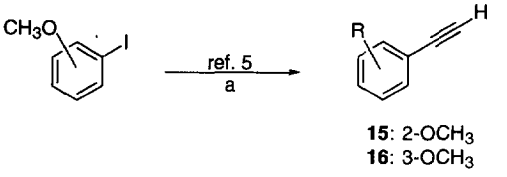
Scheme 1



Reagents: (a) (i) $(COCl)_2$, Pr_2NH or Et_2NH, toluene, r.t., (ii) $LiAlH_4$, THF, 80 °C; (b) BBr_3.

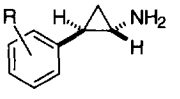
The synthesis of the *cis*-derivatives is described in Schemes 2 and 3; 2- and 3-methoxyacetylene (**15** and **16**) were prepared in 76 and 60 % yield, respectively, from 2- and 3-iodoanisole by a palladium catalyzed coupling with trimethylsilylacetylene[5] followed by removal of the trimethyl silyl group by treatment with KOH. Treatment of **15** and **16** with BuLi (THF, –70 °C) followed by addition of dimethyl carbonate provided the methyl propiolates **17** and **18** in 89 and 64 % yield, respectively (Scheme 3).

Scheme 2



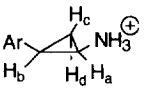
Reagents: (a) (i) trimethylsilylacetylene, Et_3N, $(PPh_3)_2PdCl_2$, CuI, r.t., (ii) 1M KOH, MeOH, r.t.

Hydrogenation of **17** and **18** over $Pd(CaCO_3)$ poisoned with 3.5 % Pb (Lindlar catalyst)[6] gave stereoselectively (*cis*/*trans* ratios were 10:1 and 19:1, respectively) the corresponding methyl propenoates **19** (91 %) and **20** (86 %). Compound **20**, but not **19**, could be purified to homogeneity by flash chromatography. However, after cyclopropanation of **19** with diazomethane under palladium catalysis (Scheme 3, Method C),[7] the isomeric impurity could be removed. The cyclopropanation of *cis*-derivatives **19** and **20** was efficient and produced only slightly lower yields than that of the corresponding *trans*-isomers.[1] The cyclopropanated products were isolated as the carboxylic acids (**21** and **22**, repectively) following alkaline hydrolysis of the ester function. Curtius rearrangement (Method D)[8] of **21** and **22** smoothly gave the primary amines **23** and **24**. A comparison of the coupling constants in the ^1H NMR spectra of **23** and **24** with those of the corresponding *trans* derivatives (**25** and **26**)[1] unambiguously established the *cis*-stereochemistry (Table 2).

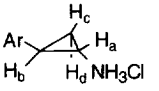


25: 2-OCH_3
26: 3-OCH_3

Table 2. ^{1}H NMR Spectroscopic Data of some *cis*- and *trans*-2-Arylcyclopropylamines.



23 and **24**



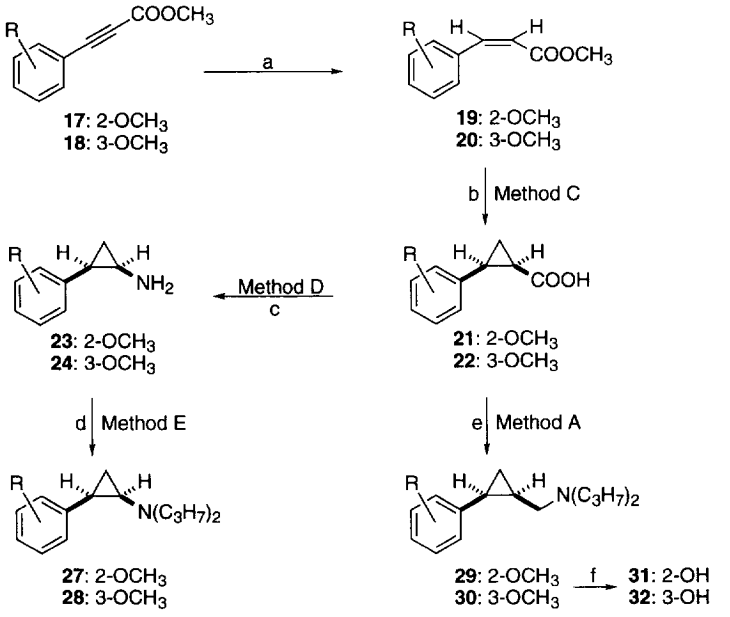
25 and **26**

compd	δ_a	δ_b	δ_c	δ_d	J_{ab}	J_{ac}	J_{ad}	J_{bc}	J_{bd}	J_{cd}
23[a]	2.95	2.36	1.21	1.38	7.9	4.2	7.3	7.3	9.2	–6.8
24[b]	2.91	2.46	1.29	1.36	7.9	4.4	7.4	7.5	9.3	–6.8
25[c]	2.52	2.75	1.35	1.31	3.5	10.1	6.8	4.4	7.8	–6.6
26[c]	2.35	2.82	1.40	1.30	3.6	10.1	6.7	4.4	7.8	–6.7

[a]Hydrochloride salt. [b]Salt with oxalic acid. [c]Data from ref. 1.

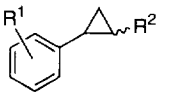
N,N-Dipropylation of **23** and **24** (Method E) gave **27** and **28**, respectively. Attempts to O-demethylate **27** and **28** with BBr_3 or 48 % aqueous HBr, were unsuccessful because of decomposition of the *cis*-arylcyclopropylamine moiety. The *cis*-1-[2-(methoxyphenyl)cyclopropyl]methylamine derivatives **29** and **30** were prepared from **21** and **22** by Method A. Methoxy derivatives **29** and **30** were conveniently O-demethylated by treatment with BBr_3 (Method B).

Scheme 3



Reagents: (a) H_2, $Pd(CaCO_3)$ + 3.5 % Pb, quinoline, toluene, r.t.; (b) (i) CH_2N_2, $Pd(OAc)_2$, CH_2Cl_2, 0 °C, (ii) NaOH, H_2O, MeOH, THF, r.t.; (c) (i) Et_3N, EtOCOCl, acetone, –10 °C, (ii) NaN_3, –10 °C, (iii) Δ (100 °C), (iv) *t*-BuOH, 90 °C, (v) HCl, H_2O, 100 °C, (d) PrI, K_2CO_3, acetonitrile, r.t.; (e) (i) $(COCl)_2$, Pr_2NH, toluene, r.t., (ii) $LiAlH_4$, THF, 80 °C; (f) BBr_3.

Table 3. Affinities of some arylcyclopropane derivatives for 5-HT_{1A} receptors.



Compd	Relative stereochem	R^1	R^2	K_i (nM)[a,b]	SEM
(1*R*,2*S*)-1[c]	trans	2-OH	NPr_2	4.9	
(1*R*,2*S*)-2[c]	trans	3-OH	NPr_2	2.6	
(1*R*,2*S*)-3[c]	trans	2-MeO	NPr_2	17	
(±)-9	trans	2-MeO	CH_2NPr_2	239	± 32
(±)-10	trans	2-MeO	CH_2NEt_2	431	± 94
(±)-11	trans	3-MeO	CH_2NPr_2	310	± 34
(±)-12	trans	2-OH	CH_2NPr_2	752	± 47
(±)-13	trans	2-OH	CH_2NEt_2	506	± 24
(±)-14	trans	3-OH	CH_2NPr_2	186	± 11
(±)-27	cis	2-MeO	NPr_2	>10000	
(±)-28	cis	3-MeO	NPr_2	736	± 110
(±)-29	cis	2-MeO	CH_2NPr_2	998	± 43
(±)-30	cis	3-MeO	CH_2NPr_2	388	± 99
(±)-31	cis	2-OH	CH_2NPr_2	379	± 71
(±)-32	cis	3-OH	CH_2NPr_2	58	± 6.5

[a]Inhibition of specific [^{3}H]-OH-DPAT binding at 5-HT_{1A} receptors in rat hippocampal membranes. [b]n= 2-4. [c]Data obtained from ref 9, included for comparison.

The affinity of the novel derivatives was lower (**32**) or much lower than that of the previously reported[1] arylcyclopropylamines (1*R*,2*S*)-**1** - **3** (Table 3).[9] Thus, it appears that a *cis*-configuration of the arylcyclopropylamine moiety positions the arylethylamine chain in a conformation which is unfavourable for an efficient interaction with the 5-HT_{1A} receptor binding site. Alternatively, or in addition, the steric bulk of the cyclopropane ring may prevent an optimal receptor interaction. The low affinity of the *trans*-substituted dialkylaminomethyl derivatives reflects the importance for a relatively short distance between the aromatic ring and the basic nitrogen.[10]

The racemic *cis*-derivative **32** had a K_i value of 58 nM and was the most potent 5-HT_{1A} receptor ligand of the novel derivatives. This was not surprising because the aromatic ring, the hydroxyl group and the nitrogen of either enantiomer of **32** may be superimposed onto the same structural elements of the potent (1*R*,2*S*)-**1** when it adopts a proposed bioactive conformation.[10,11] It should be noted, however, that preliminary molecular mechanics (MMX) calculations indicate that the fitted conformations of **32** are energetically disfavoured.

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